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Final Report-98-ERI-003 Identification of Population with Lifetime ^{41}Ca-Labeled Skeletons

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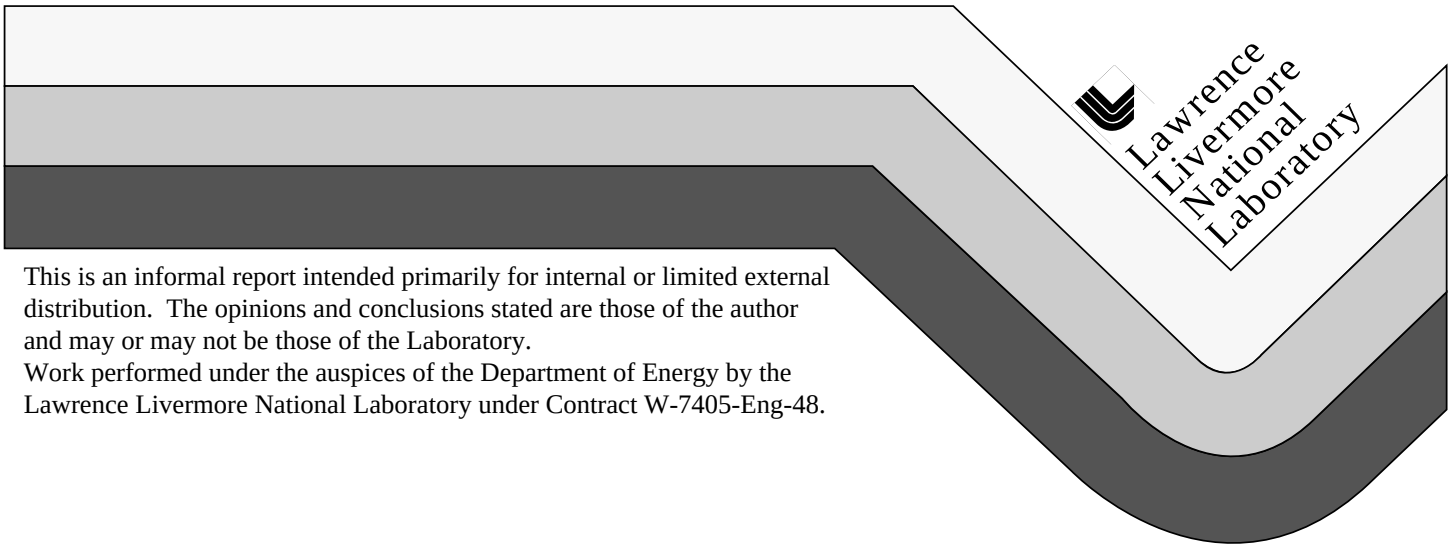

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Final Report – 98-ERI-003
Identification of Population with Lifetime ^{41}Ca-Labeled Skeletons

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In 1997 we first postulated the existence of a special human population that had had their skeletons inadvertently isotopically adulterated in the past. We theorized that the population, and the necessary LLNL accelerator mass spectrometer (AMS) measurement technology, would prove a significant resource in the fight to combat osteoporosis. This LDRD project was to establish such. The project was significantly successful in its initial year, but was not renewed for another and the research is now ended at LLNL.

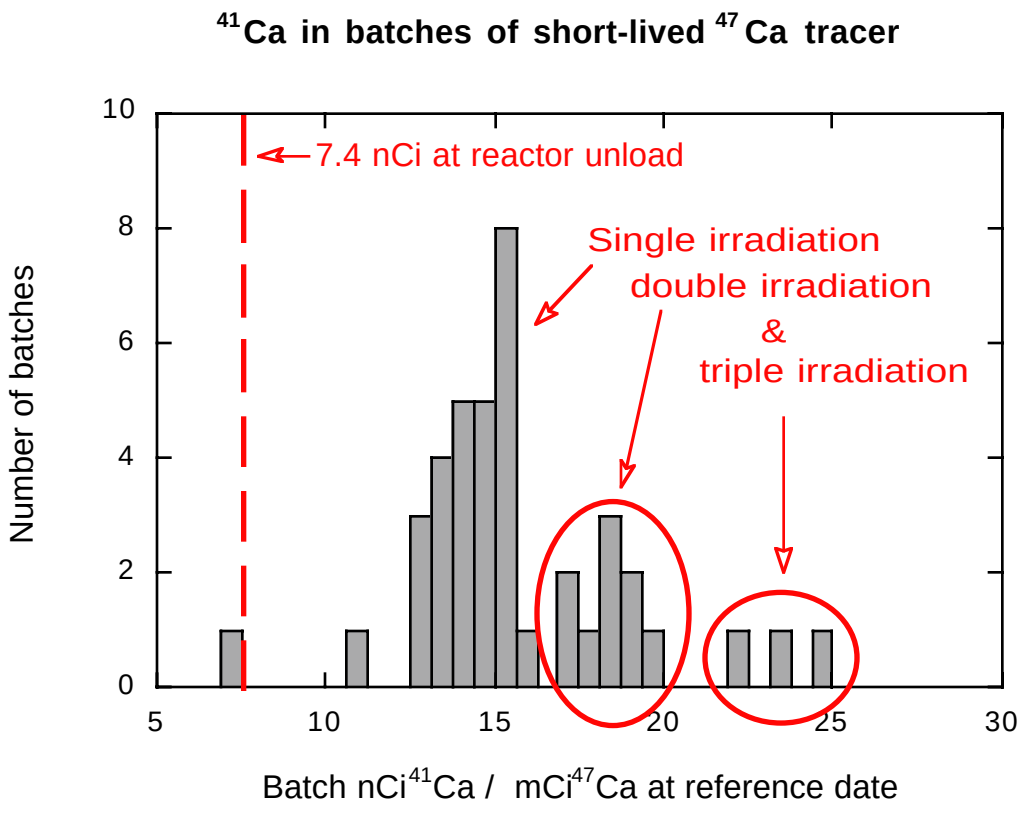
Osteoporosis is a major public health problem. In the United States alone, there are over a million osteoporotic fractures a year; these have an attendant annual financial cost of more than $10 billion. Consequently, there are considerable efforts to develop therapies and a great need for better diagnostic tools.

Osteoporosis is a disease characterized by reduced bone mineral density (BMD). Skeletal calcium deposition and resorption are usually closely coupled, but prolonged slight net imbalances ultimately deplete the skeleton. Many current therapies are directed at redressing this imbalance by partially blocking bone resorption. The evaluation of these, and of other therapies more generally, requires good measurements of skeletal calcium loss. However, the current x-ray techniques are insensitive to changes and the preferred alternative techniques of using urine/serum proxy biomarkers only poorly predict an individual's BMD. The goal of this project was to establish a potentially more powerful method for monitoring bone degradation: the direct measurement of resorbed and excreted skeletal calcium. This promises better, faster, and less-expensive development of therapies.

Recent work has demonstrated the necessary labeling of the human skeleton with an isotope novel to calcium kinetics research, ^{41}Ca, coupled with ultrasensitive AMS detection in processed urine of the minute amounts of the tracer resorbed and excreted in any day. Although a single tracer administration can usefully label the skeleton for life, a significant outstanding issue was that it might take years of normal skeletal remodeling before the ^{41}Ca signal of resorption would usefully reflect skeletal resorption. However, we realized that historical experimental subjects had received previously unrecognized ^{41}Ca tracer as an impurity in other radiotracers in unrelated experiments performed by other researchers even many years in advance. Thus, it transpires that there exist thousands of one-time experimental subjects who, by virtue of having been accidentally labeled sufficiently long ago, now have skeletons with thoroughly equilibrated tracer. If even a small fraction of this unique population were available for enrollment into contemporary protocols, then these subjects might prove the ideal population for evaluation of osteoporosis therapies. At the very least, measurements of existing historical samples would provide unique fundamental bone kinetics data, as for the first time the long-term evolution of a calcium bolus can be monitored, and in a population sufficient for epidemiology at that.

We proposed a three-year program to (1) confirm the magnitude and extent of historical ^{41}Ca dosing, (2) exactly characterize the long-term ^{41}Ca signal by comparing it with conventional measurements of skeletal health, and (3) demonstrate the utility of the historically labeled population in evaluating an actual potential therapy for osteoporosis. However, rather than investigate historical records to learn the identity of those inadvertently dosed, find them, and if possible enroll them into a new protocol, this project was to be particularly efficient by making use of a multiyear archive of samples from original, inadvertent ^{41}Ca-dosing experiments at Creighton University in Omaha, Nebraska. Because the subjects had been dosed in conventional studies of calcium kinetics, much important correlating historical data would also be available for comparison. Measurements of contemporary urine samples specifically provided for this project by selected identified subjects would follow.

To confirm widespread ^{41}Ca dosing, during FY98 we investigated the neutron irradiation genesis and administration of the ^{41}Ca impurity in the original radiotracers. This involved researching the historical use of the impure short-lived ^{45}Ca and ^{47}Ca radiotracers in bioavailability studies and investigations of metabolic bone diseases in general, reconstructing the historical Creighton University experiments from records in particular, and the analysis of historical radiotracer dosing solutions from the Creighton archive. The necessary new protocols for preparing the solutions were developed in collaboration with University of



California at Davis scientists also. The ^{41}Ca impurities in ^{47}Ca radiotracer is graphed

below. That the impurities are greater than the calculated 7.4 nCi ^{41}Ca per mCi ^{47}Ca based on an understanding of the manufacturing process, is due to the week of ^{47}Ca decay between tracer reactor unload and the tracer delivery to the administering scientist by the reference calibration date. The unphysical low result is ascribed to imperfect Creighton historical records. The tracer manufacturer acknowledges re-irradiating unsold ^{47}Ca tracer, which presumably accounts for the two groupings of more impure tracer each about an additional 7.4 nCi irradiation greater than the last group. Knowing the tracer ^{41}Ca levels and the historical administration of the solutions it is possible to calculate the distribution of ^{41}Ca administrations. It transpires that ^{45}Ca is less ^{41}Ca impure than is ^{47}Ca, as expected based on their different manufacture, but that ^{45}Ca, the more widely employed of the impure radiotracers, is up to an order of magnitude more impure than anticipated.

Thus, knowing the amounts of ^{41}Ca historically administered, and the results of our separate experiments with deliberately administered ^{41}Ca tracer, it is possible to derive the expected long-term level of excreted resorbed ^{41}Ca and to the estimate the lifetime radiological dose to the historical subjects. We conclude that the 10,000 or so subjects were dosed with variable but typically large enough amounts of ^{41}Ca that should result in a measurable signal today. Happily, the likelihood is that none of the historical subjects has been adversely affected by their inadvertent radiological exposure. We ultimately obtained permission to analyze archived actual human samples, but measurement of these samples was delayed by lengthy deliberations on the ethical and legal implications.

However, we did discover a second archive at the University of Texas Southwestern Medical Center. This is potentially a better source of material as the samples were generated in numerous historical evaluations of actual osteoporosis therapies in which ^{41}Ca-impure radiotracers were used. The therapies might now powerfully be retrospectively evaluated, both to contribute to our understanding of the therapies and to highlight the potential of the use of ^{41}Ca tracer and LLNL measurement.

The opportunities for osteoporosis research as a consequence of the work to date have been described in a submitted Letter to Nature.

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